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Title:

BENZOYL UREA COMPOUNDS, PROCESS FOR THEIR
PRODUCTION, AND ANTITUMOROUS COMPOSITIONS
CONTAINING THEM ;

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Inventor(s):

WATANABE MASAHIRO (JP); YOKOYAMA KAZUMASA (JP); HAGA
TAKAHIRO (JP); KONDO NOBUO (JP); KOYANAGI TORU (JP);
SUGI HIDEO (JP); NAKAJIMA TSUNETAKA (JP); YAMADA
NOBUTOSHI (JP) ;

Applicant(s): ISHIHARA MINING _CHEMICAL CO (JP) ;

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ABSTRACT:

A benzoyl urea compound having the formula: (I) wherein A is a bromine
atom or a chlorine atom.



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(73) Proprietor: **ISHIHARA SANGYO KAISHA LTD.**
No. 3-11, Edobori 1-chome
Nishi-ku Osaka-shi Osaka 550(JP)

Proprietor: **GREEN CROSS CORPORATION**
15-1, Imabashi-1-chome Higashi-ku Osaka-
shi
Osaka 541(JP)

(72) Inventor: **Kondo, Nobuo**
12-303, Kawanakashinmachi
Daito-shi Osaka(JP)
Inventor: **Nakajima, Tsunetaka**
1330-61, Gojonomachi
Kashiwara-shi Nara-ken(JP)
Inventor: **Watanabe, Masahiro**
570-22, Okuradanishimizu
Akashi-shi Hyogo-ken(JP)
Inventor: **Yokoyama, Kazumasa**
7-2-201, Terauchi 2-chome
Toyonaka-shi Osaka(JP)

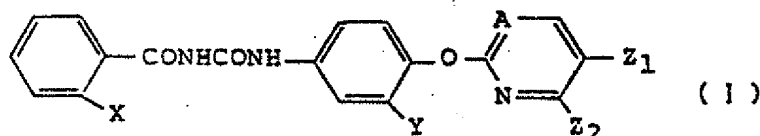
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Inventor: **Suyama, Tadakazu**
3-7, Matsuigaoka 4-chome
Tanabe-cho Tsuzuki-gun Kyoto(JP)
Inventor: **Haga, Takahiro**
84-7, Hirai-cho
Kusatsu-shi Shiga-ken(JP)
Inventor: **Yamada, Nobutoshi**
321-31, Fuke-cho
Moriyama-shi Shiga-ken(JP)
Inventor: **Sugi, Hideo**
321-31, Fuke-cho
Moriyama-shi Shiga-ken(JP)
Inventor: **Koyanagi, Toru**
3F-410, 151-30, Ninomaru-cho Mukaijima
Fushimi-ku Kyoto-shi Kyoto(JP)

Ⓓ Representative: **Wächtershäuser, Günter, Dr.**
Tal 29
W-8000 München 2(DE)

Description

The present invention relates to an antitumour pharmaceutical composition containing a benzoyl urea compound as the main component. More particularly, the present invention relates to a pharmaceutical composition whereby the absorbability of an antitumour benzoyl urea compound of the formula:



wherein X is a halogen atom or a nitro group, each of Y and Z₂ is a hydrogen atom or a halogen atom, Z₁ is a halogen atom or a trifluoromethyl group, and A is a =CH-group or a nitrogen atom, through e.g. mucous membranes of the gut, is improved.

The benzoyl urea compounds of the formula I are known to have excellent antitumour activities (Japanese Unexamined Patent Publication No. 109721/1982). However, these compounds are hardly soluble in water, and accordingly their absorbability through e.g. the gut is poor. Therefore, in order to obtain adequate antitumour activities, it is necessary to increase the dose, whereby there is a possible danger of adverse effects due to the excessive administration.

It is known that fatty oil is useful as a solvent for injection purposes (F. Stürner, Einführung in die Verfahrenstechnik der Arzneiformung, 1973, page 270). Further, it is known that polyethylene glycol is useful as a solvent or as an ointment base (The Merck Index, 10th edition, 1983, 7441). Further, it has been described that a cyclodextrine can be used for improvement of solubility and increase of concentration of a drug in blood (Angew. Chem. Int. Ed. Engl. 19, 1980, 356-358).

It is an object of the present invention to provide a pharmaceutical composition whereby the absorbability of the benzoyl urea compound of the formula I through the skins or mucous membranes of the gut and rectum is improved.

The present inventors have studied various additives with an aim to improve the absorbability of the benzoyl urea compound of the formula I through the skins or mucous membranes of the gut and rectum, and have finally found that certain specific substances, i.e. cyclodextrins, polyethylene glycols and refined oils, are capable of improving the absorbability of the benzoyl urea compound of the formula I through mucous membranes, particularly, from the gut and rectum.

Thus, the present invention provides a pharmaceutical composition as defined in claim 1 comprising a benzoyl urea compound of the formula I and at least one member selected from a dimethyl β -type cyclodextrin, a polyethylene glycol and a refined oil.

Now, the present invention will be described in detail with reference to the preferred embodiments.

In the accompanying drawings, Figure 1 is a comparative graph showing the solubility of Compound No. 1 in aqueous solutions of various cyclodextrins, wherein ■ designates α -type cyclodextrin, □ designates γ -type cyclodextrin and ● designates β -type cyclodextrin.

Figure 2 is a comparative graph showing the solubility of Compound No. 2 in aqueous solutions of various cyclodextrins, wherein ■, □ and ● are as defined in respect of Figure 1.

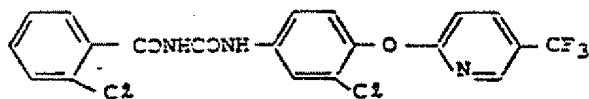
Figure 3 is a graph showing the change with time of the concentration of Compound No. 3 in the plasma when the compound dispersed in various cyclodextrins was orally administered, wherein ○ designates the control, Δ designates β -type cyclodextrin having a concentration of 1.7%, ⊙ designates dimethyl β -type cyclodextrin having a concentration of 40%, and □ designates dimethyl β -type cyclodextrin having a concentration of 2%.

Figure 4 is a graph showing the change with time of the concentration of Compound No. 2 in the plasma when the compound dispersed in various solvents was orally administered, wherein ○ designates the control, ● designates polyoxyethylene hardened castor oil, ■ designates Tween 80®, □ designates polyethylene glycol 400, and ⊙ designates dimethyl β -type cyclodextrin.

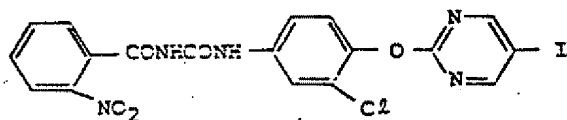
In this specification, the halogen atom is preferably a chlorine atom or a bromine atom.

The following compounds may be mentioned as typical examples of the benzoyl urea compound of the formula I.

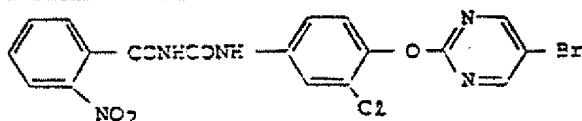
Compound No. 1: (Melting point: 182 - 185°C)



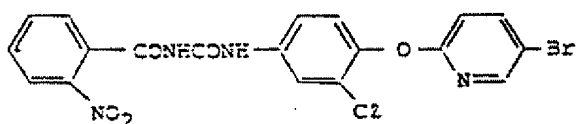
Compound No. 2: (Melting point: 235 - 238°C)



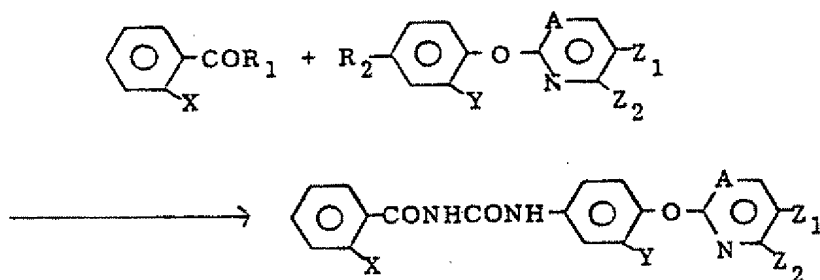
Compound No. 3: (Melting point: 229 - 231°C)



Compound No. 4: (Melting point: 207 - 208°C)



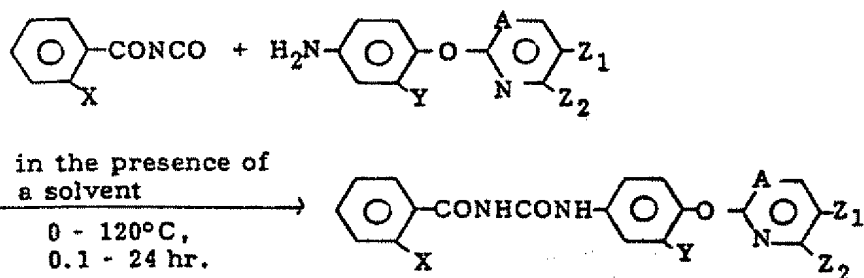
The benzoyl urea compounds may be prepared, for instance, by the following process:



wherein X, Y, Z₁, Z₂ and A are as defined above, and each of R₁ and R₂ is an isocyanate group or an amino group, provided that R₁ and R₂ are different from each other.

Specifically, the following processes may be mentioned.

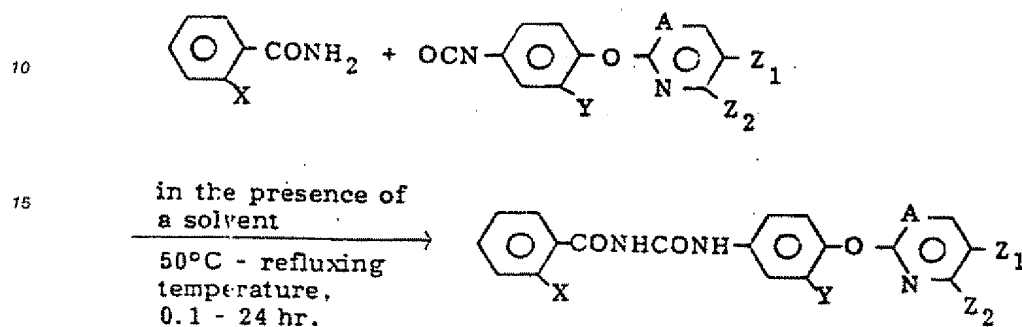
[A]



wherein X, Y, Z₁, Z₂ and A are as defined above.

As the solvent to be used in the above reaction, octane, benzene, toluene, xylene, monochlorobenzene, dimethylsulfoxide or ethyl acetate may be mentioned.

[B]

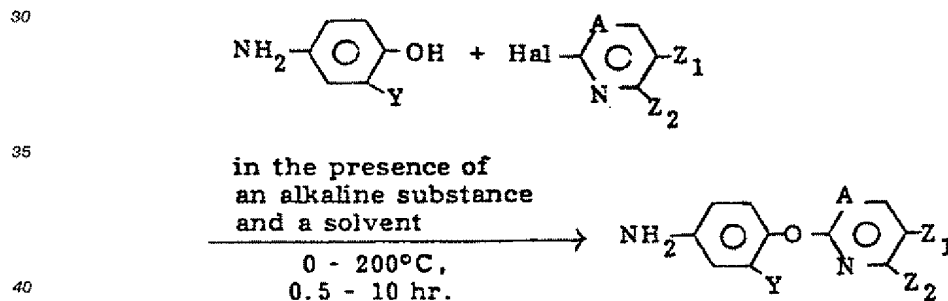


wherein X, Y, Z₁, Z₂ and A are as defined above.

The solvent to be used in the above reaction is the same as one used in the reaction [A].

The aniline compound or the phenyl isocyanate compound used as the starting material in each of the above reactions, may be prepared, for instance, by the following processes.

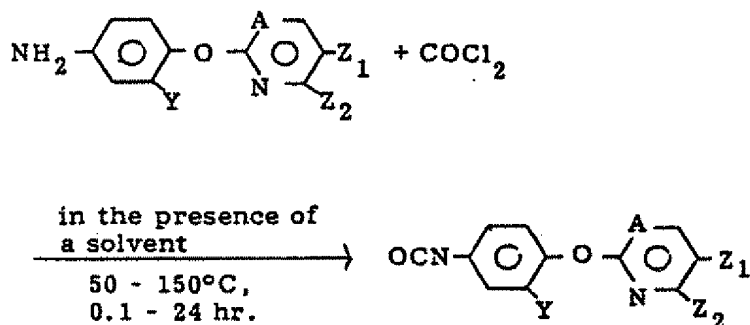
[C]



wherein Hal is a halogen atom, and Y, Z₁, Z₂ and A are as defined above.

As the alkaline substance to be used in the above reaction, sodium hydroxide, potassium hydroxide, sodium carbonate or potassium carbonate may be mentioned. As the solvent, there may be mentioned an aprotic polar solvent such as dimethylsulfoxide, dimethylformamide, hexamethylphosphoramide or sulfolane, or a ketone such as acetone, methyl ethyl ketone or methyl isobutyl ketone.

[D]



15 wherein Y, Z₁, Z₂ and A are as defined above.

As the solvent to be used in the above reaction, a solvent inert to phosgene, such as toluene, xylene, monochlorobenzene, ethyl acetate or dioxane, may be mentioned.

Now, a specific example for the preparation of a benzoyl urea compound to be used in the present invention, will be presented.

Synthetic Example

Synthesis of Compound No. 3:

25 N-(2-nitrobenzoyl)-N'-[4-(5-bromo-2-pyrimidinyl)oxy]-3-chlorophenyl]urea

(1) Into a flask, 10.0 g of 5-bromo-2-chloropyrimidine, 7.42 g of 4-amino-2-chlorophenol, 14.26 g of potassium carbonate and 100 ml of dimethylsulfoxide were introduced, and reacted in a nitrogen atmosphere at 120°C for 2.5 hours under stirring. After the completion of the reaction, the product was poured into water, and extracted with ethyl acetate. The extract was washed with water and a saturated sodium chloride aqueous solution, dried over anhydrous sodium sulfate, and then purified by silica gel column chromatography, whereby 12.26 g of oily 4-(5-bromo-2-pyrimidinyl)oxy-3-chloroaniline was obtained.

(2) Into a flask, a solution obtained by dissolving 12.26 g of the above 4-(5-bromo-2-pyrimidinyl)oxy-3-chloroaniline in 45 ml of dioxane, was introduced, and a solution obtained by dissolving 8.64 g of 2-nitrobenzoyl isocyanate in 45 ml of dioxane, was dropwise added thereto, and then the mixture was reacted at room temperature for 5 hours. After the completion of the reaction, the product was poured into water, subjected to filtration and washed with hot water. The crystals thereby obtained were washed with ethyl acetate, methylene chloride and methanol, to obtain 13.5 g of the desired product having a melting point of from 229 to 231°C.

40 The cyclodextrin to be employed in the present invention, is a dimethyl β-type cyclodextrin. The cyclodextrin is incorporated in an amount of from 0.01 to 100 parts by weight, preferably from 0.1 to 10 parts by weight, relative to 1 part by weight of the benzoyl urea compound of the formula I. This combination is particularly preferred for the preparation of a solid formulation, and suitable for use for the preparation of tablets, granules or suppositories.

45 As the polyethylene glycol, it is usual to employ a polyethylene glycol having an average molecular weight of from 200 to 20,000, preferably from 200 to 4,000. The concentration of the benzoyl urea compound of the formula I in the polyethylene glycol is adjusted at a level of from 5 to 50 mg/ml, preferably from 10 to 30 mg/ml. This composition is suitable for the formulation for rectal administration such as a suppository, or for the formulation of external application such as an ointment.

50 As the refined oil, there may be mentioned vegetable oils such as soybean oil, safflower oil, sesame oil or olive oil, and glycerides such as medium-chain length fatty acid triglycerides (wherein the medium-chain length fatty acids are preferably straight chained or branched fatty acids having from 8 to 10 carbon atoms, such as caprylic acid or capric acid) [for example, ODO® (manufactured by Nisshin Seiyu K.K.), Coconard RK, MT (manufactured by Kao Food K.K.)]. The refined oil is an oil purified to such an extent that it is useful for a pharmaceutical. The refined oil is incorporated in such an amount that the concentration of the benzoyl urea compound of the formula I in the refined oil will be from 5 to 500 mg/ml, preferably from 20 to 200 mg/ml. This composition is suitable for the preparation of soft capsules. In the case where the refined oil is employed, the solubility is further improved by incorporating non-ionic surfactants. Preferred non-ionic

surfactants are a polyoxyethylene-polyoxy propylene copolymer (pluronic), a glycerin fatty acid ester, a sorbitol fatty acid ester, a propylene glycol fatty acid ester, a sucrose fatty acid ester, a polyethylene glycol fatty acid ester, Tween 80 or a polyoxyethylene hardened castor oil. The surfactant is incorporated usually in an amount of from 1 to 50% (weight/volume), preferably from 2 to 10% (weight/volume) of the total amount.

The pharmaceutical composition of the present invention may be formulated in accordance with the conventional methods for formulations. For instance, a liquid formulation may be filled in suitable capsules to obtain capsule drugs. Further, the liquid formulation may be freeze-dried or spray-dried to obtain a dried formulation. The dried formulation may be formed into tablets, capsules, enteric drugs, granules, powders, suppositories or ointments by the conventional methods for drug formulations.

As will be shown in Test Examples 1 and 2, the dimethyl β -type cyclodextrins increase the solubility of the benzoyl urea compound of the formula I in water, and thus they are believed to increase the absorption of the benzoyl urea compound by the gut.

As will be shown in Test Examples 3 and 4, by suspending the benzoyl urea compound of the formula I in aqueous solutions of dimethyl β -type cyclodextrins, the concentration of the benzoyl urea compound of the formula I in the plasma after the oral administration is distinctly higher as compared with the control.

Further, also in the case where the polyethylene glycols or refined oils are incorporated, it is likewise evident that the absorption of the benzoyl urea compound of the formula I by the gut is facilitated.

By using the pharmaceutical composition of the present invention, it is possible to reduce the dose of the benzoyl urea compound of the formula I and thus to reduce the side effects or the pain to the patient when it is administered.

Thus, the pharmaceutical composition of the present invention makes it possible to provide an effective formulation of the benzoyl urea compound of the formula I which has not been possible by the conventional method for formulations, and thus opens a new way for medical and clinical developments.

Test Example 1 (Solubility)

0.1 μ mol of Compound No. 1 or No. 2 was added to 1 ml of an aqueous solution of each cyclodextrin with a concentration of from 0 to 8 mM, and the mixture was shaken at 25°C for 100 hours. After completion of the shaking, the mixture was filtered through a millipore filter of 0.45 μ m to obtain a filtrate. The dissolved Compound No. 1 or No. 2 was quantitatively analyzed by a high speed liquid chromatography under the conditions identified below, and the solubility was obtained. The obtained solubilities are shown in Figures 1 and 2.

Operational conditions for the liquid chromatography

Separation column:	As the packing material, octadecylated silica gel was filled in a stainless steel tube having an internal diameter of from 0.39 to 4.6 mm and a length of from 100 to 300 mm.
Column temperature:	30°C
Mobile phase:	Mixture of acetonitrile-water (the mixing ratio was adjusted so that the eluting time of the drug becomes from 5 to 10 minutes).
Flow rate:	1 ml/min.
Wave length for detection:	265 nm

Test Example 2 (Solubility)

7.5 mg of Compound No. 3 was added to 1 ml of an aqueous solution of each cyclodextrin at various concentrations or to 1 ml of polyethylene glycol 400, and the solubility of Compound No. 3 at 25°C was obtained in the same manner as in Test Example 1. The results thereby obtained are shown in Table 1.

Table 1

Additives	Concentrations (mg/ml)	Solubility of Compound No. 3 (μ g/ml)
Aqueous solution containing no additives	-	0.024
α -Type cyclodextrin (Ref.)	14.6	0.164
Dimethyl α -type cyclodextrin (Ref.)	17.5	0.294
β -Type cyclodextrin (Ref.)	17.0	1.64
Dimethyl β -type cyclodextrin	20.0	24.1
(Invention)	140	5180
"	500	7440
Trimethyl β -type cyclodextrin (Ref.)	21.4	1.00
"	100	13.4
"	200	30.4
Polyethylene glycol 400 (Invention)	100%	7500

Test Example 3 (Absorbability through the gut)

20 mg of Compound No. 3 was taken into a mortar, and 5 ml of an aqueous solution containing 1.7% of β -type cyclodextrin or 2% or 40% of dimethyl β -type cyclodextrin was added under stirring to obtain a suspension of Compound No. 3. The suspension was orally administered by an oral sonde to a group of three Wistar male rats (body weight: 200 - 250 g). The dose of Compound No. 3 was 20 mg/kg rat body weight. Further, Compound No. 3 was likewise suspended in an aqueous solution containing 0.5% of sodium salt of carboxymethyl cellulose, and the suspension was used as the control (O in Figure 3). After the administration, the blood was periodically sampled, and the plasma was separated. After the removal of protein by acetonitrile, Compound No. 3 in the plasma was quantitatively analyzed by a high speed liquid chromatography as shown in Test Example 1. The change with time of the concentration of Compound No. 3 in the plasma after the administration is shown in Figure 3.

In the case of 40% dimethyl β -type cyclodextrin, the concentration in the plasma was as high as about 3.5 times the concentration obtained by the control. Test Example 4 (Absorbability through the gut)

The changes with time of the concentration of Compound No. 3 in the plasma after the oral administration were studied in the same manner as in Test Example 3 by using an aqueous solution of 10% (weight/volume) Polysolvate 80 (Tween 80, manufactured by Nakayai Kagaku K.K.), 10% (weight/volume) polyoxyethylene hardened castor oil 60 (manufactured by Nikko Chemical K.K.), 100% polyethylene glycol 400 or 50% (weight/volume) dimethyl β -type cyclodextrin, as the dispersing solvent for Compound No. 3, and an aqueous solution of 0.5% (weight/volume) sodium salt of carboxymethyl cellulose, as the control. The results are shown in Figure 4. The concentration of Compound No. 3 in the plasma was about 7.5 times

in the case of dimethyl β -type cyclodextrin and about 5 times in the case of polyethylene glycol 400, as compared with the control.

Test Example 5 (Absorbability through the gut)

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The changes with time of the concentration of Compound No. 3 in the plasma after the oral administration were studied in the same manner as in Test Example 3 by using an aqueous solution of 10% (weight/volume) hydroxypropyl cellulose (HPC-L, manufactured by Nippon Soda Co., Ltd.), 2.5% (weight/volume) methyl cellulose (Metrose SM 15, manufactured by Shin-Etsu Chemical Co., Ltd.), 10% (weight/volume) hydroxypropylmethyl cellulose (Metrose TC5R, manufactured by Shin-Etsu Chemical Co., Ltd.), 2.5% (weight/volume) sodium salt of carboxymethyl cellulose (manufactured by Wako Junyaku K.K.), 10% (weight/volume) sucrose fatty acid ester (P1570, manufactured by Hishito K.K.) or 10% (weight/volume) Pluronic F 68 (manufactured by Asahi Denka Kogyo K.K.), as an aqueous dispersing solvent for Compound No. 3, and medium-chain length fatty acid triglyceride (ODO, manufactured by Nisshin Seiyu K.K.), ODO containing 5% (weight/volume) sucrose fatty acid ester (S-370F, manufactured by Hishito K.K.), or a refined soybean oil (The Green Cross Corporation) or refined sesame oil (Takemoto Yushi K.K.) containing 5% (weight/volume) of S-370F, as a non-aqueous dispersing solvent, and an aqueous solution of 50% (weight/volume) dimethyl β -type cyclodextrin and an aqueous solution of 0.5% (weight/volume) sodium carboxymethyl cellulose, as the control. The results are shown in Table 2.

Among the aqueous dispersing solvents, 50% (weight/volume) dimethyl β -type cyclodextrin showed the highest absorption, and among the non-aqueous dispersing solvents, the refined soybean oil or refined sesame oil containing 5% (weight/volume) sucrose fatty acid ester showed a high absorption almost equal to dimethyl β -type cyclodextrin. Further, ODO containing 5% (weight/volume) Pluronic F32 showed a high absorption.

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Table 2

	Concentration in the plasma ($\mu\text{g/ml}$)			
	1 hr	3 hrs	5 hrs	24 hrs
10% (weight/volume) hydroxypropyl cellulose	0.05	0.12	0.11	0.04
2.5% (weight/volume) methyl cellulose	0.06	0.11	0.11	0.03
10% (weight/volume) hydroxypropylmethyl cellulose	0.14	0.31	0.28	0.10
2.5% (weight/volume) sodium salt of carboxymethyl cellulose	0.04	0.11	0.09	0.09
10% (weight/volume) sucrose fatty acid ester	0.04	0.18	0.18	0.24
10% (weight/volume) Pluronic F68	0.11	0.19	0.23	0.12
Medium-chain length fatty acid triglyceride (ODO)	0.12	0.17	0.21	0.24
5% (weight/volume) sucrose fatty acid ester/ODO	0.06	0.18	0.20	0.22
5% (weight/volume) sucrose fatty acid ester/refined soybean oil	0.12	0.50	0.55	0.39
5% (weight/volume) sucrose fatty acid ester/refined sesame oil	0.14	0.49	0.57	0.37
5% (weight/volume) Pluronic F31/ODO	0.10	0.20	0.22	0.47
0.5% (weight/volume) sodium salt of carboxymethyl cellulose	0.03	0.10	0.15	0.01
50% (weight/volume) Dimethyl β -type cyclodextrin	0.28	0.58	0.49	0.36

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Test Example 6

A Witepsol W-35 suppository (weight: about 45 mg) comprising 1.8 mg of Compound No. 3 and 12.5% (weight/volume) of dimethyl β -type Cyclodextrin, was administered to the rectum of each Wistar male rat having a body weight of about 90 g (a group of three rats). Then, the blood was periodically sampled from the jugular vein, and the concentration of Compound No. 3 in the plasma was measured. To a control group, a suppository containing no cyclodextrin was administered. The results are shown in Table 3. It is evident that by the addition of dimethyl β -type cyclodextrin, the absorbability of Compound No. 3 increased.

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Table 3

	Concentration in the plasma ($\mu\text{g/ml}$)				
	0	0.5 hr	1 hr	2 hrs	4 hrs
Control	0	0.04	0.08	0.11	0.09
Dimethyl β -type cyclodextrin	0	0.32	0.48	0.94	0.99

Test Example 7

The capsules prepared in Example 3 corresponding to 20 mg/kg of Compound No. 3 were orally administered to three beagle dogs (male: body weight: 5 kg). Then, the blood was periodically sampled from the branchium vein, and the concentration of Compound No. 3 in the plasma was measured. To the control group, a suspension of Compound No. 3 (20 mg/ml) in an aqueous solution containing 0.5% of sodium salt of carboxymethyl cellulose was administered. The results are shown in Table 4. It is evident that in the present invention, the absorbability of Compound No. 3 increased.

Table 4

	Concentration in the plasma ($\mu\text{g/ml}$)				
	0	0.5 hr	1 hr	2 hrs	4 hrs
Control	0	0.03	0.07	0.10	0.09
Polyethylene glycol 400	0	0.37	0.61	1.12	1.11

Test Example 8

The acute toxicity, the dose and the administration method were studied with respect to the formulations obtained by the present invention.

Acute toxicity

BDF₁ mice (male, female, 25 - 27 g) or SD rats (male, female, 250 - 270 g) were used in a group of 10 animals. To these animals, the formulations prepared in Examples 1 to 6 were orally administered in the form of a liquid suspension, at a dose of 50 mg/kg of the benzoyl urea compound of the formula I. The animals were observed for 7 days, whereby no instance of death was observed. On the other hand, the same results were obtained when the substrate material only or the benzoyl urea compound of the formula I only was suspended in water and orally administered.

Dose

The dose may be varied depending upon the subject to be treated, the degree of the disease or other conditions for administration, and can not simply be prescribed. However, a daily dose is usually from about 0.1 to about 100 mg/kg of the active ingredient.

Administration method

The pharmaceutical composition of the present invention may be administered through oral, rectal or cutaneous route in various formulations as mentioned above.

Test Example 9

The pharmacological activities of the pharmaceutical compositions of the present invention were

studied. Among the formulations of Examples 1 to 6, the results of the study on the formulation of Example 3 are shown in Table 5.

To BDF₁ mice (male, 28 - 22 g), L-1210 leukemia cells were intraperitoneally inoculated in an amount of 1×10^6 cells/mouse. One day later and 4 days later, a test drug was orally administered. It was difficult to administer the drug in the final formulation form, and therefore Compound No. 3, polyethylene glycol 400 and the substrate were mixed and administered to each mouse in the form of a liquid suspension in an amount of 0.5 ml. Thereafter, the mice was observed for survival or death. As a result, the antitumour activities of Compound No. 3 was distinctly observed only when it was administered together with the substance specified in the present invention. Within the dose range of Compound No. 3 at this time, no antitumour activities were observed when polyethylene glycol 400 was absent. Namely, the results indicate the transfer of Compound No. 3 from the gut into the blood in Test Example 7, and thus reflect an improvement in the absorbability of Compound No. 3 by the composition of the present invention.

The improvement in the absorbability of the benzoyl urea compound of the formula I through the gut by the readily absorbable pharmaceutical composition of the present invention (see Test Examples 3, 4 and 5), is believed to substantially contribute to the effective antitumour activities of the compound.

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Table 5

Administered formulation *	T/C (%) **
Polyethylene glycol 400 + substrate + Compound No. 3	
<u>Dose of Compound No. 3 (mg/kg)</u>	
50	95
25	183
12.5	134
6.25	120
Substrate + Compound No. 3	
<u>Dose of Compound No. 3 (mg/kg)</u>	
50	103
25	101
12.5	102
6.25	102
Polyethylene glycol 400 alone	103
Substrate only	101
Physiological sodium chloride solution (Control)	100

*: Formulation of Example 3

$$45 \quad ** : T/C(\%) = \frac{\text{Median survival time of test animals}}{\text{Median survival time of control animals}} \times 100$$

EXAMPLE 1

50

1.8 mg of Compound No. 3 was dispersed under heating in a suppository substrate comprising 90% by weight of polyethylene glycol 1000, 4% of polyethylene glycol 4000 and 6% of polyethylene glycol 400, and formed into a suppository by a suppository-forming mold.

55 EXAMPLE 2

1.8 mg of Compound No. 3 was dispersed under heating in a Witepsol W-35 suppository substrate (about 45 mg) containing 12.5% (weight/volume) dimethyl β -type cyclodextrin, and formed into a suppository.

tory.

EXAMPLE 3

- 5 Compound No. 3 was dissolved in polyethylene glycol 400 to bring the concentration to a level of 20 mg/ml, and soft gelatin capsules (an average weight: 600 mg) were prepared in accordance with a usual method (Tsuda Kyosuke et al., Iyaku Kaihatsu Kisokoza 11 Yakuzai Seizoho (Jo) p 347, Gigin Shokan).

EXAMPLE 4

- 10 Soft gelatin capsules were prepared in the same manner as in Example 3 except that a refined soybean oil, refined sesame oil or refined safflower oil containing 5% (weight/volume) of Pluronic F31, was used instead of polyethylene glycol 400.

EXAMPLE 5

- 15 A small amount of water was added to 4 g of Compound No. 3 and 125 g of dimethyl β -type cyclodextrin, and the mixture was kneaded and granulated by an extrusion granulation method, and then packed into hard gelatin capsules to obtain a capsule drug for oral administration.

EXAMPLE 6

- 20 To the granules obtained in Example 3, 1% of magnesium stearate was added, and the mixture was compressed and tableted to obtain a tablet drug for oral administration.

EXAMPLE 7

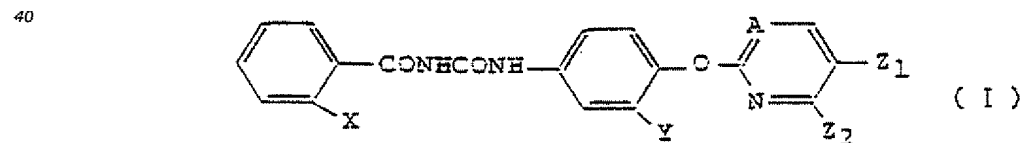
- 25 A suppository was prepared in the same manner as in Example 1 except that Compound No. 1 was used instead of Compound No. 3.

EXAMPLE 8

- 30 A capsule drug was prepared in the same manner as in Example 5 except that Compound No. 2 was used instead of Compound No. 3.

Claims

- 35 1. A pharmaceutical composition comprising a benzoyl urea compound having the formula:



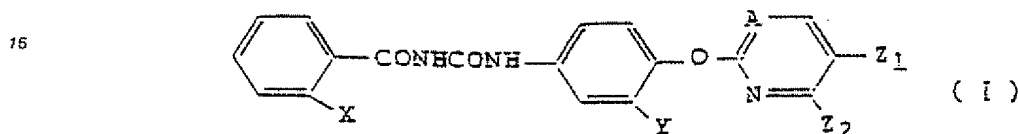
- wherein X is a halogen atom or a nitro group, each of Y and Z₂ is a hydrogen atom or a halogen atom, Z₁ is a halogen atom or a trifluoromethyl group, and A is a =CE-group or a nitrogen atom, and at least one member selected from a dimethyl β -type cyclodextrin which is incorporated in an amount of from 0.01 to 100 parts by weight relative to one part by weight of the benzoyl urea compound, a polyethylene glycol, which is incorporated in such an amount that the concentration of the benzoyl urea compound is from 5 to 50 mg/ml of the polyethylene glycol, and a mixture of a refined oil and a non-ionic surfactant, which is incorporated in such an amount that the concentration of the benzoyl urea compound is from 5 to 500 mg/ml of the refined oil.

- 50 2. The pharmaceutical composition according to Claim 1, wherein the benzoyl urea compound is N-(2-nitrobenzoyl)-N'-[3-chloro-4-(5-halogeno-2-pyrimidinyl)oxy]phenyl]urea.

3. The pharmaceutical composition according to Claim 1, wherein the benzoyl urea compound is N-(2-nitrobenzoyl)-N'-[3-chloro-4-(5-bromo-2-pyrimidinylloxy)phenyl]urea.
4. The pharmaceutical composition according to Claim 1, wherein the polyethylene glycol has an average molecular weight of from 200 to 20,000.
5. The pharmaceutical composition according to Claim 1, wherein the refined oil is a vegetable oil or a glyceride.

10 Revendications

1. Composition pharmaceutique Comprenant un composé de benzoyl urée, représenté par la formule :



20

dans laquelle :

- X est un atome d'halogène ou un groupe nitro ;
- Y et Z₂ représentent chacun un atome d'hydrogène ou un atome d'halogène ;
- Z₁ est un atome d'halogène ou un groupe trifluorométhyle; et
- A est un groupe =CH- ou un atome d'azote,

25

et au moins un élément choisi parmi une diméthyl cyclo dextrine de type β , qui est incorporée dans une quantité de 0,01 à 100 parties en poids pour une partie en poids du composé de benzoyl urée, un polyéthylène glycol, qui est incorporé dans une quantité telle que la concentration du composé de benzoyl urée soit de 5 à 50 mg/ml du polyéthylène glycol, et un mélange d'une huile raffinée et d'un agent tensio-actif non-ionique, qui est incorporé dans une quantité telle que la concentration du

30

2. Composition pharmaceutique selon la revendication 1, dans laquelle le composé de benzoyl urée est la N-(nitro-2 benzoyl) N'-[chloro-3 (halogéno-5 pyrimidinylloxy-2)-4 phényl] urée.

35

3. Composition pharmaceutique selon la revendication 1, dans laquelle le composé de benzoyl urée est la N-(nitro-2 benzoyl)N'-[chloro-3 (bromo-5 pyrimidinylloxy-2)-4 phényl] urée.

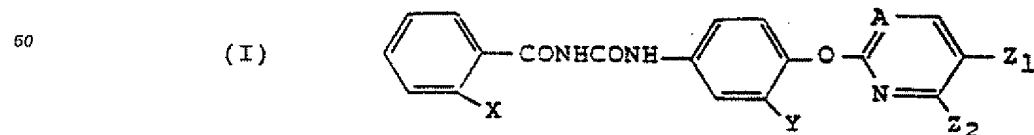
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4. Composition pharmaceutique selon la revendication 1, dans laquelle le polyéthylène glycol a une masse moléculaire moyenne de 200 à 20 000.

5. Composition pharmaceutique selon la revendication 1, dans laquelle l'huile raffinée est une huile végétale ou un glycéride.

45 Patentansprüche

1. Pharmazeutische Zusammensetzung, umfassend eine Benzoylharnstoff-Verbindung der Formel:



55

worin

X ein Halogenatom oder eine Nitrogruppe ist, jedes von Y und Z₂ eine Wasserstoff- oder ein Halogenatom ist,

Z₁ ein Halogenatom oder eine Trifluormethylgruppe ist und

A eine =CH-Gruppe oder ein Stickstoffatom ist, und

mindestens einen Bestandteil, ausgewählt aus

einem Dimethyl- β -cyclodextrin in einer Menge von 0,01 bis 100 Gew.-Teilen auf 1 Gew.-Teil der Benzoylharnstoff-Verbindung,

einem Polyethylenglycol in einer solchen Menge, daß die Konzentration der Benzoylharnstoff-Verbindung 5 bis 50 mg/ml des Polyethylenglycols beträgt und einer Mischung aus einem raffinierten Öl und einem nicht-ionischen, grenzflächenaktiven Mittel in einer solchen Menge, daß die Konzentration der Benzoylharnstoff-Verbindung 5 bis 500 mg/ml des raffinierten Öls beträgt.

2. Pharmazeutische Zubereitung nach Anspruch 1, worin die Benzoylharnstoff-Verbindung N-(2-Nitrobenzoyl)-N'-[3-chlor-4-(5-halogen-2-pyrimidinylloxy)phenyl]harnstoff ist.
3. Pharmazeutische Zubereitung nach Anspruch 1, worin die Benzoylharnstoff-Verbindung N-(2-Nitrobenzoyl)-N'-[3-chlor-4-(5-brom-2-pyrimidinylloxy)phenyl]harnstoff ist.
4. Pharmazeutische Zubereitung nach Anspruch 1, worin das Polyethylenglycol ein mittleres Molekulargewicht von 200 bis 20.000 hat.
5. Pharmazeutische Zubereitung nach Anspruch 1, worin das raffinierte Öl ein vegetarisches Öl oder ein Glycerid ist.

FIGURE 1

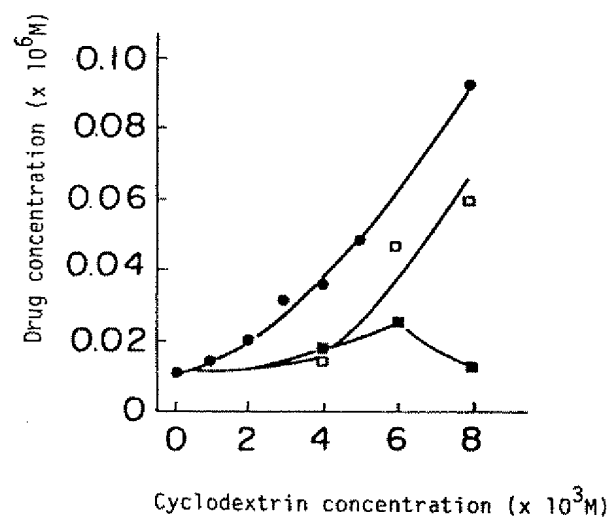


FIGURE 2

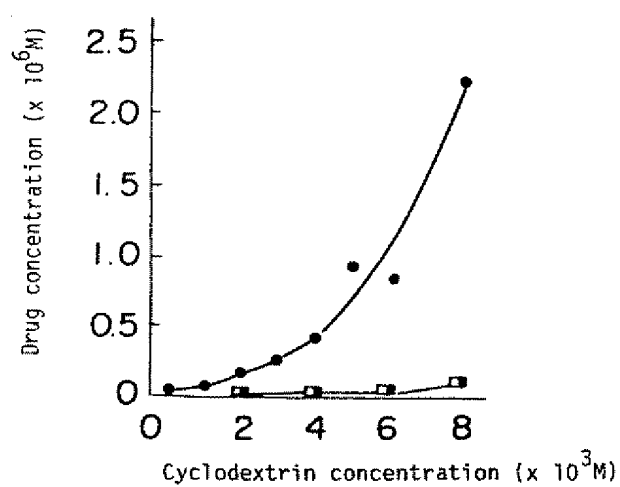


FIGURE 3

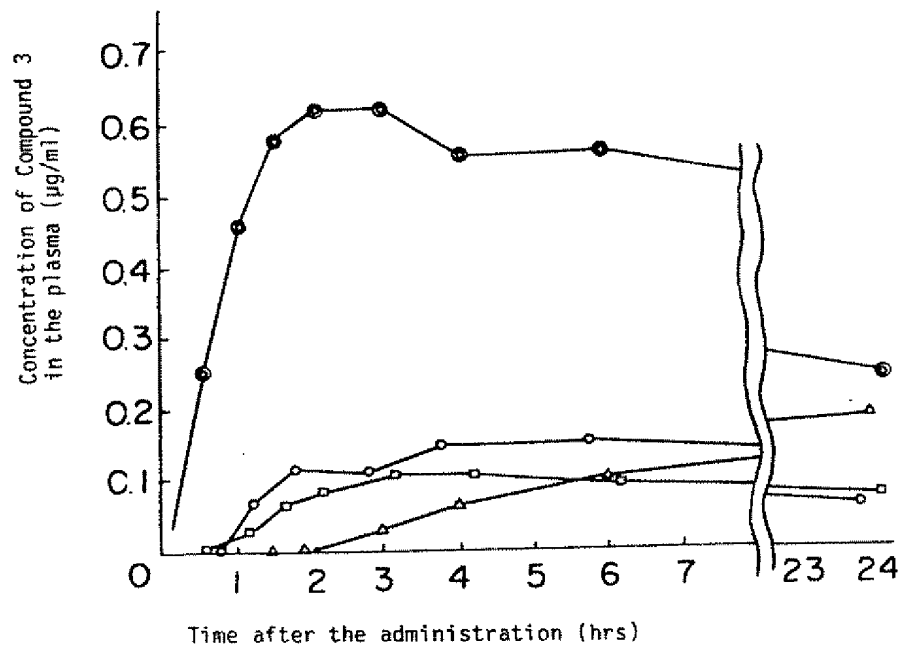


FIGURE 4

